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# Long-Term Prognostic Value of Less Stringent Electrocardiographic Q Waves and Fourth Universal Definition of Myocardial Infarction Q Waves

**Running Title:** Polcwiartek *et al.*; Electrocardiographic Q-Wave Criteria and Mortality Risk

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## Abstract

**BACKGROUND:** The Fourth Universal Definition of Myocardial Infarction defines electrocardiographic (ECG) Q waves as duration  $\geq 30$ ms and amplitude  $\geq 1$ mm or QS complex in two contiguous leads. However, current taskforce criteria may be overly restrictive. Therefore, we investigated the association of isolated, lenient, or strict Q waves with long-term outcome.

**METHODS:** From 2001–2015, we included Danish primary care patients with digital ECGs that were evaluated for Q waves. If none occurred, patients had no Q waves. If no other contiguous Q wave occurred, patients had isolated Q waves. If another contiguous Q wave occurred meeting only one criterion ( $\geq 30$ ms and  $< 1$ mm or  $< 30$ ms and  $\geq 1$ mm), patients had lenient Q waves. If another contiguous Q wave occurred, patients had strict Q waves.

**RESULTS:** Of 365,206 patients, 87,957 had isolated, lenient, or strict Q waves (24%; median age, 61 years; male, 48%), and 277,249 had no Q waves (76%; median age, 53 years; male, 42%). Mortality risk was increased with isolated (all-cause adjusted hazard ratio [aHR], 1.33; 95% confidence interval [CI], 1.29–1.37; cardiovascular-cause aHR, 1.78; 95% CI, 1.70–1.87), lenient (all-cause aHR, 1.41; 95% CI, 1.33–1.50; cardiovascular-cause aHR, 1.78; 95% CI, 1.63–1.94), or strict (all-cause aHR, 1.64; 95% CI, 1.57–1.72; cardiovascular-cause aHR, 2.70; 95% CI, 2.52–2.89) Q waves compared with no Q waves. Highest mortality risk was associated with antero-septal lenient or strict Q waves.

**CONCLUSIONS:** This large contemporary analysis suggests that less stringent Q-wave criteria carry prognostic value in predicting adverse outcome among primary care patients.

**KEYWORDS:** Electrocardiogram; Fourth Universal Definition of Myocardial Infarction; Myocardial infarction; Primary care; Q wave; Epidemiology.

## Clinical Significance

- Among primary care patients with digital electrocardiograms, any Q wave whether isolated, lenient, or strict was associated with increased long-term mortality risk compared with no Q waves.
- These findings may help in reclassifying patients currently considered at low cardiovascular risk to a different risk category where additional testing and medical intervention could be necessary.

## Introduction

Q waves on the electrocardiogram (ECG) are highly suggestive of prior or silent and potentially unrecognized myocardial infarction and are associated with larger infarct size as assessed on cardiac magnetic resonance imaging (MRI).<sup>1,2</sup> Detection of Q waves is clinically important as their emergence carry prognostic value of future cardiovascular disease burden.<sup>3-7</sup>

Over the years, various Q-wave criteria have emerged, with the most recent recommended in the 2018 consensus document the Fourth Universal Definition of Myocardial Infarction<sup>8</sup> (Table 1). From a cardiovascular risk stratification standpoint, strict Q waves (duration  $\geq 30$  ms and amplitude  $\geq 1$  mm or QS complex in two contiguous leads), as defined by current taskforce criteria, may be overly restrictive, particularly among patients with cardiovascular risk factors or subclinical cardiovascular disease. In contrast, isolated Q waves, where Q waves in a contiguous lead are absent, may represent an incidental finding and be of limited prognostic value.<sup>3</sup> However, to date, no real-world evidence is available on the clinical importance of lenient Q waves meeting only one criterion (duration  $\geq 30$  ms and amplitude  $< 1$  mm or duration  $< 30$  ms and amplitude  $\geq 1$  mm).

The clinical approach to patients with Q waves raising the suspicion of prior or silent and potentially unrecognized myocardial infarction is to do imaging studies with echocardiogram or cardiac MRI to determine whether myocardial infarction occurred or not. However, in primary care, such additional testing is not accessible without specialist referral, and delayed access to outpatient care and potentially delayed initiation of cardiovascular preventive interventions may worsen outcomes. Therefore, detecting less stringent Q-wave criteria in primary care may be beneficial in early cardiovascular risk stratification and referral purposes.

Using a large contemporary clinical database including nearly 1 million digital ECGs from primary care patients from the greater Copenhagen area in Denmark, we investigated the mortality risk associated with isolated, lenient, or strict Q waves using current taskforce criteria.

## Methods

### Study Design and Population

This was a Danish register-based cohort study including the most recent available ECG from primary care patients referred to the central core facility Copenhagen General Practitioners' Laboratory from 2001 to 2015.<sup>9,10</sup> All 12-lead ECGs were recorded at rest and in supine position, digitally stored in the MUSE Cardiology Information System, and processed and automatically scored using the Marquette 12SL algorithm (GE Healthcare, Chicago, IL, USA).<sup>11</sup> Trained ECG technicians have manually described all ECGs that further have been over read by a consultant cardiologist. Data on age and sex were obtained from the Danish Civil Registration System<sup>12</sup> and vital status from the Danish Register of Causes of Death.<sup>13</sup>

Patients with missing demographic data were excluded, so were those  $< 16$  years, as the 12SL algorithm applies pediatric as opposed to adult criteria in this group. Patients were also excluded if they were erroneously registered with a death date prior to ECG recording. Furthermore, using 12SL algorithm statements, we excluded ECGs of poor quality, with pacemaker rhythms, and not qualified for suitable Q-wave interpretation, mainly applying to ECG abnormalities causing axis deviation, as incidental Q waves may occur.<sup>14</sup> This included bradycardia or tachycardia (heart rate  $< 50$  or  $> 120$  beats per min, respectively),

Sokolow-Lyon or Cornell voltage criteria for left ventricular hypertrophy, atrial fibrillation, junctional rhythm, retrograde conduction, second- or third-degree atrioventricular block, premature atrial or ventricular complexes, ventricular rhythms, fascicular or bundle branch blocks, and delta waves.

### Q-Wave Subtypes

In accordance with current task force criteria, Q waves were defined in any two leads of a contiguous lead grouping: inferior (II with aVF), (III with aVF), and (aVF with II or III); anteroseptal (V1 with V2), (V2 with V1 or V3), (V3 with V2 or V4), and (V4 with V3 or V5); and anterolateral (V5 with V4 or V6), (V6 with V5), (I with aVL), and (aVL with I).

Using 12SL algorithm measurements, ECGs were evaluated for Q waves (duration  $\geq 30$  ms and amplitude  $\geq 1$  mm or QS complex [Q amplitude  $> 0$  mm and R amplitude = 0 mm]) in each of the leads II, III, aVF, V1–V6, I, and aVL. If none occurred, patients had no Q waves (Figure 1A). If no other Q wave occurred in a contiguous lead, patients had isolated Q waves (Figure 1B). If another Q wave occurred in a contiguous lead meeting only one criterion (duration  $\geq 30$  ms and amplitude  $< 1$  mm or duration  $< 30$  ms and amplitude  $\geq 1$  mm), patients had lenient Q waves (Figure 1C). If another Q wave occurred in a contiguous lead, patients had strict Q waves (Figure 1D). Of note, patients may demonstrate more than one Q-wave subtype, thus the total of isolated, lenient, and strict Q waves sums to  $> 100\%$ .

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### Comorbidities, Procedures, and Cardiovascular Drugs

To further exclude ECGs with potential pacemaker rhythms, we used the Danish National Patient Register<sup>15</sup> to identify patients with a prior pacemaker or implantable cardioverter-defibrillator using International Classification of Diseases (ICD) and Nordic Classification of Surgical Procedures (NCSP) codes, whichever came first. Furthermore, we used ICD codes in the Danish National Patient Register to identify heart failure, myocardial infarction, atrial fibrillation, valvular heart disease, hypertension, diabetes, chronic obstructive pulmonary disease, and chronic kidney disease diagnosed prior to ECG recording. We also used NCSP codes to identify percutaneous coronary intervention for myocardial infarction, radiofrequency ablation for atrial fibrillation, aortic or mitral valve surgery for valvular heart disease, and renal replacement therapy for chronic kidney disease.

Using Anatomical Therapeutic Chemical (ATC) codes in the Danish National Prescription Register,<sup>16</sup> filled prescriptions of cardiovascular drugs were identified within 180 days prior to ECG recording. Usually, hypertension, diabetes, and chronic obstructive pulmonary disease are managed in primary care, and patients may not necessarily have ICD codes registered. Therefore, prior filled prescriptions of antihypertensives (at least dual therapy), antidiabetics, and beta adrenergic or anticholinergic inhalants were further used to define these comorbidities, respectively.<sup>17</sup> See Supplementary Table 1 (available online) for ICD, NCSP, and ATC codes.

### Outcome Measure

The ECG recording represented the baseline of our study. The main outcome was all-cause mortality, and we performed an additional analysis using death from any cardiovascular cause (ICD-8, 400–451; ICD-10, I00–

99). Patients were followed for up to 2 years until outcome or censoring in case of emigration, end of follow-up, or end of study on December 31, 2017, whichever came first.

## Statistical Analysis

Continuous variables were reported as medians with 25th–75th percentiles and categorical variables as counts with percentages. Differences were compared using Mann-Whitney U and chi-squared tests, as appropriate.

Cumulative incidence of mortality for no, isolated, lenient, or strict Q waves was computed and displayed using the Kaplan-Meier method. Cox regression was used to compute hazard ratios (HRs) with 95% confidence intervals (CIs) for mortality risk associated with isolated, lenient, or strict Q waves, with no Q waves as reference. The proportional hazard assumption was tested by plotting cumulative Martingale residuals and was not violated. Interaction testing was based on introducing an interaction term in a Cox regression model and using a likelihood ratio test to compare this model with one without an interaction term. A two-sided *P*-value <0.01 was considered statistically significant for interactions and <0.05 for all other analyses. Linearity of continuous variables was also assessed using a likelihood ratio test comparing a linear description with a categorical one. Age was observed to violate linearity and was included as a categorical variable based on quartiles. Analyses were adjusted for age quartiles, sex, heart failure, myocardial infarction, atrial fibrillation, valvular heart disease, hypertension, lipid-lowering drugs, diabetes, chronic obstructive pulmonary disease, and chronic kidney disease.

Data management and analysis were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA) and R, version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

## Ethics

The Danish Data Protection Agency approved use of data (reference: 2007-58-0015, internal reference: GEH-2014-014, I-Suite number: 02732). By Danish law, ethical approval is not required for retrospective register-based studies.

## Results

### Patient Characteristics

We included 365,206 patients, of which 87,957 (24%) had isolated, lenient, or strict Q waves, and 277,249 (76%) had no Q waves (Supplementary Figure 1, available online). Patients with isolated, lenient, or strict Q waves were older (median age, 61 years) and more often male (48%) than patients with no Q waves (median age, 53 years; male, 42%). Patients with isolated, lenient, or strict Q waves also demonstrated higher comorbidity burden and more often filled cardiovascular drug prescriptions. Although statistically significant, no clinical differences in ECG characteristics were observed between groups (Table 2).

Among the 87,957 patients with isolated, lenient, or strict Q waves, 74,726 patients (85%) had isolated Q waves localized in inferior (*n*=44,047; 59%), anteroseptal (*n*=22,875; 31%), and anterolateral (*n*=13,908; 19%)



leads. A total of 14,373 patients (16%) had lenient Q waves localized in inferior ( $n=11,259$ ; 78%), anteroseptal ( $n=853$ , 6%), and anterolateral ( $n=2579$ , 18%) leads. Finally, 17,165 patients (20%) had strict Q waves localized in inferior ( $n=10,142$ ; 59%), anteroseptal ( $n=7015$ , 41%), and anterolateral ( $n=1487$ , 9%) leads (Supplementary Table 2, available online). Of note, 17,454 patients (20%) demonstrated more than one Q-wave subtype, of which 11,314 patients (65%) had isolated and lenient Q waves, 3081 patients (18%) had isolated and strict Q waves, 2206 patients (13%) had lenient and strict Q waves, and 853 patients (5%) had isolated, lenient, and strict Q waves.

### Mortality Risk by Q-Wave Subtypes

During 2-year follow-up, a total of 8312 patients (10%) with isolated, lenient, or strict Q waves died from all causes compared with 12,664 patients (5%) with no Q waves (Figure 2). This was similar with cardiovascular mortality ( $n=3728$ , 4% vs  $n=4615$ , 2%).

Following multivariable adjustment, mortality risk remained increased for isolated (all-cause HR, 1.33; 95% CI, 1.29–1.37; cardiovascular-cause HR, 1.78; 95% CI, 1.70–1.87), lenient (all-cause HR, 1.41; 95% CI, 1.33–1.50; cardiovascular-cause HR, 1.78; 95% CI, 1.63–1.94), or strict (all-cause HR, 1.64; 95% CI, 1.57–1.72; cardiovascular-cause HR, 2.70; 95% CI, 2.52–2.89) Q waves compared with no Q waves in any two leads of a contiguous lead grouping. We observed similar findings by inferior, anteroseptal, and anterolateral leads, with highest mortality risk associated with lenient (all-cause HR, 1.77; 95% CI, 1.51–2.08; cardiovascular-cause HR, 2.66; 95% CI, 2.12–3.33) or strict (all-cause HR, 1.89; 95% CI, 1.78–2.00; cardiovascular-cause HR, 3.12; 95% CI, 2.85–3.40) anteroseptal Q waves (Figure 3).

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### Sensitivity Analyses

We performed various sensitivity analyses to test the consistency and robustness of our findings.

First, we investigated mortality risk in each of the leads II, III, aVF, V1–V6, I, and aVL, and while isolated Q waves in leads III, aVF, and V5 were of limited prognostic value, findings from remaining leads resembled the main analysis (Supplementary Figure 2, available online).

Second, we tested whether age, sex, and prior myocardial infarction modified the association of isolated, lenient, or strict Q waves with all-cause mortality risk. No interactions were observed, and effect sizes were similar by subgroups (Supplementary Figure 3–5, available online).

Third, although we accounted for ECG abnormalities and comorbidities commonly associated with axis deviation, residual axis deviation may potentially affect findings. Therefore, we performed an additional subgroup analysis of patients with normal axis between  $-30^\circ$  and  $+90^\circ$  ( $n=343,780$ ; 94%), and mortality risk was more pronounced (Supplementary Figure 6, available online).

Fourth, we observed that no additional prognostic value was gained when lenient Q waves were stratified by duration ( $\geq 30$  ms and  $< 1$  mm) and amplitude ( $< 30$  ms and  $\geq 1$  mm) criteria (Supplementary Figure 7, available online).

Fifth, according to current taskforce criteria, the likelihood of myocardial infarction is increased if ST-T deviations occur in the same leads as Q waves. We observed that mortality risk increased dramatically when criteria for ST depression, ST elevation, or inverted T waves were concomitantly present (Supplementary Figure 8, available online).

## Discussion

In this large-scale nationally representative study of real-world primary care patients, we report a series of key findings underscoring that additional prognostic value may be gained by considering less stringent Q-wave criteria than those recommended in the Fourth Universal Definition of Myocardial Infarction. First, in any two leads of a contiguous lead grouping, we demonstrated that 16% of patients with lenient Q waves, of which 14% did not have concomitant strict Q waves, were potentially misclassified as not having excess cardiovascular risk according to current taskforce criteria. Second, we demonstrated similar prognostic value between lenient and strict Q waves, with nearly a 2-fold increased mortality risk in anteroapical leads. Importantly, the prognostic value did not differ when lenient Q waves were stratified by duration and amplitude criteria. Third, although the majority of patients demonstrated isolated Q waves, these were associated with differential prognostic value. Fourth, all findings were consistent when excluding the few patients with residual axis deviation. Finally, we demonstrated that mortality risk increased by more than 2-fold when ST-T deviations accompanied isolated, lenient, or strict Q waves, thus potentially reflecting higher coronary artery disease burden.

The ECG plays a pivotal role in diagnosing and managing myocardial infarction owing to universal availability and low costs. However, if myocardial infarction is not timely diagnosed or silent and potentially unrecognized, the prognosis is poor, with increased risks of heart failure and mortality. While prior studies have investigated and debated the utility of isolated or strict Q waves,<sup>3-7</sup> no contemporary studies have described whether additional prognostic value may be gained by considering lenient Q waves. Our novel findings can easily be integrated into current clinical practice and suggest that, in addition to strict Q waves, clinicians should be aware when observing lenient Q waves regardless of location. Of note, prior studies have reported a rather comparable prognosis between inferior and anterior Q waves.<sup>3, 6</sup> Considering current clinical practice, we speculate that particularly patients with lenient Q waves are not recognized as candidates for imaging studies with echocardiogram or cardiac MRI to determine whether myocardial infarction occurred or not and for cardiovascular prevention interventions, thus they potentially have accelerated incidences of myocardial infarction and heart failure, with an associated increase in mortality risk over time. In support, a recent study suggests that patients with borderline Q waves, as defined according to the Minnesota Code, have an unfavorable cardiovascular risk profile potentially associated with adverse outcome.<sup>18</sup> However, further work is warranted to explore the extent of subclinical myocardial injury, as detected by less stringent Q-wave criteria, and whether targeted cardiovascular drug therapies for myocardial infarction and heart failure including aspirin, statins, angiotensin-converting enzyme inhibitors, or beta blockers may improve prognosis in this group. It also remains unknown how patients with isolated, lenient, or strict Q waves differ regarding myocardial scar burden, structural and electrical remodeling, and left ventricular ejection fraction.

It is beyond the scope of our study to conclude whether Q waves that are wide, deep, or both matters the most. In prior studies, Q waves  $\geq 40$  ms, as defined according to the Minnesota Code, have been observed to carry a poorer prognosis than Q waves defined according to less stringent Minnesota Code criteria and to carry a comparable prognosis to Q waves defined using the Fourth Universal Definition of Myocardial Infarction.<sup>3, 6</sup> However, in a prior autopsy study, 90% of inferior myocardial infarction cases could be detected with a duration  $\geq 30$  ms rather than  $\geq 40$  ms in lead aVF.<sup>19</sup> In another study, the amplitude rather than duration measured early following myocardial infarction was associated with infarct size on cardiac MRI, although this association reversed at follow-up where duration became more strongly associated with

infarct size.<sup>20</sup> It has further been observed that a certain threshold of infarct size should be reached on cardiac MRI to detect significant Q waves.<sup>1,2</sup>

## Limitations

Our study has several limitations worth noting, particularly the observational design only allowing associations to be established, not causation. Furthermore, unmeasured and unknown confounding including cardiovascular symptoms, family history of cardiovascular disease, ethnicity, obesity, and smoking status may affect findings, but such data was unfortunately not available in our registers. However, obesity and smoking status were indirectly accounted for by adjusting analyses for hyperlipidemia and chronic obstructive pulmonary disease, respectively. Although we relied on the ECG to detect whether patients had prior or silent and potentially unrecognized myocardial infarction, echocardiography and cardiac MRI are more sensitive tools in detecting this condition, but we did unfortunately not have such data available. Finally, we identified that around 3% of all patients had a diagnosis of prior myocardial infarction in the Danish National Patient Register, and the rather low prevalence may be attributed to various reasons including Q-wave regression or silent and potentially unrecognized myocardial infarction. However, the validity of the diagnosis in the Danish National Patient Register has proven to be high.<sup>21</sup>

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## Conclusions

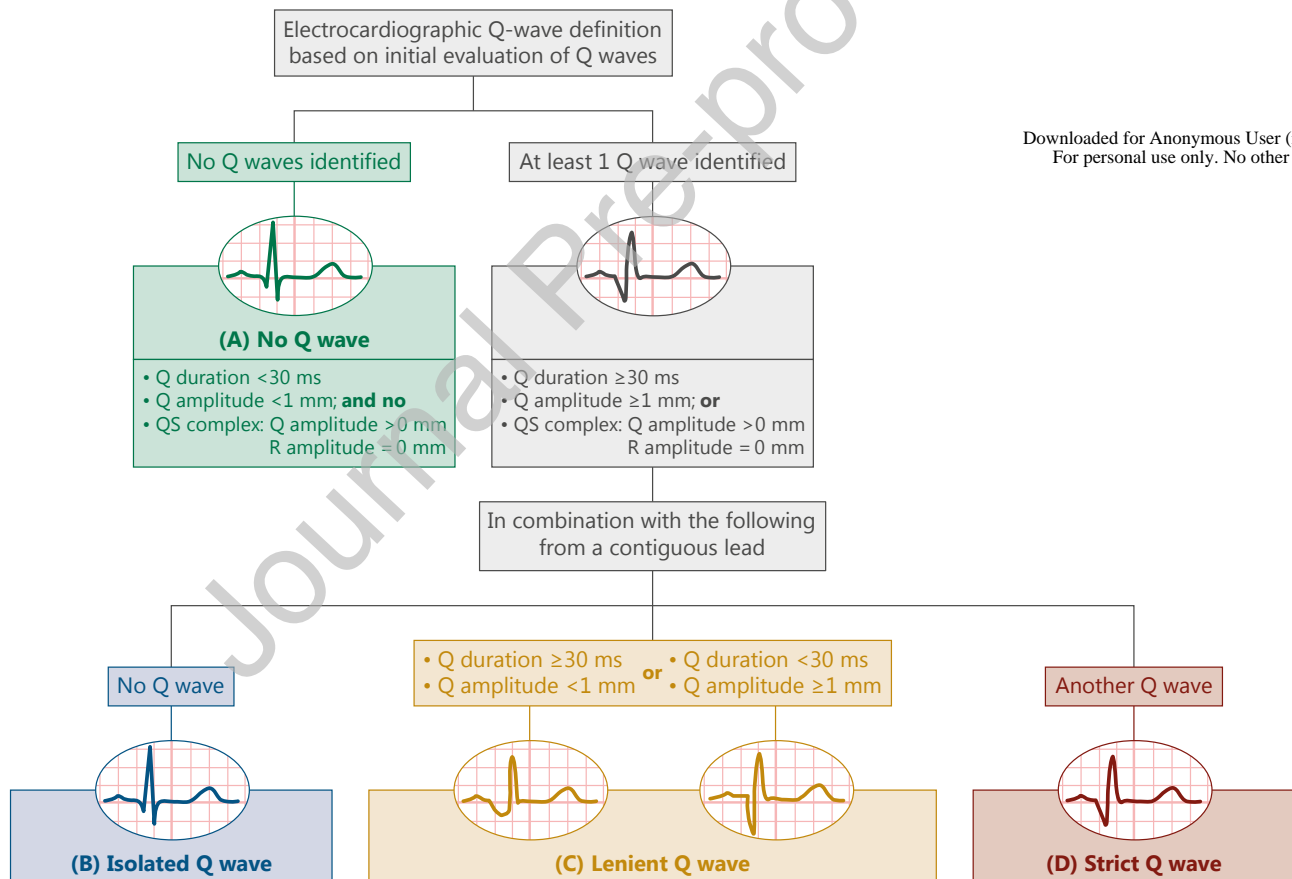
This large contemporary analysis suggests that lenient, strict, and, to a lesser extent, isolated Q waves carry prognostic value in predicting adverse long-term outcome among primary care patients. This finding has potential clinical implications for reclassifying patients currently considered at low cardiovascular risk to a different category where additional testing and medical intervention could be necessary, although further work is warranted to explore this.

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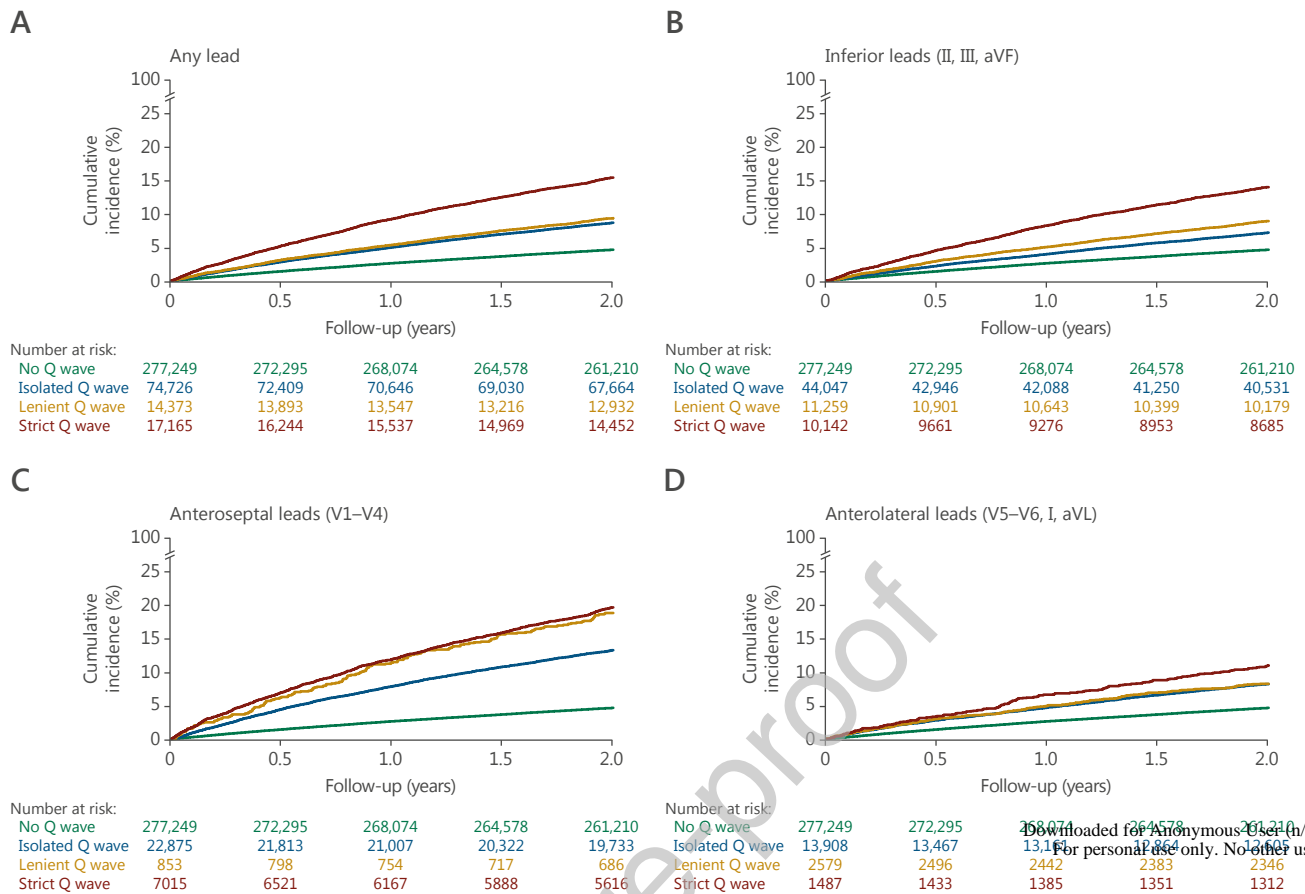
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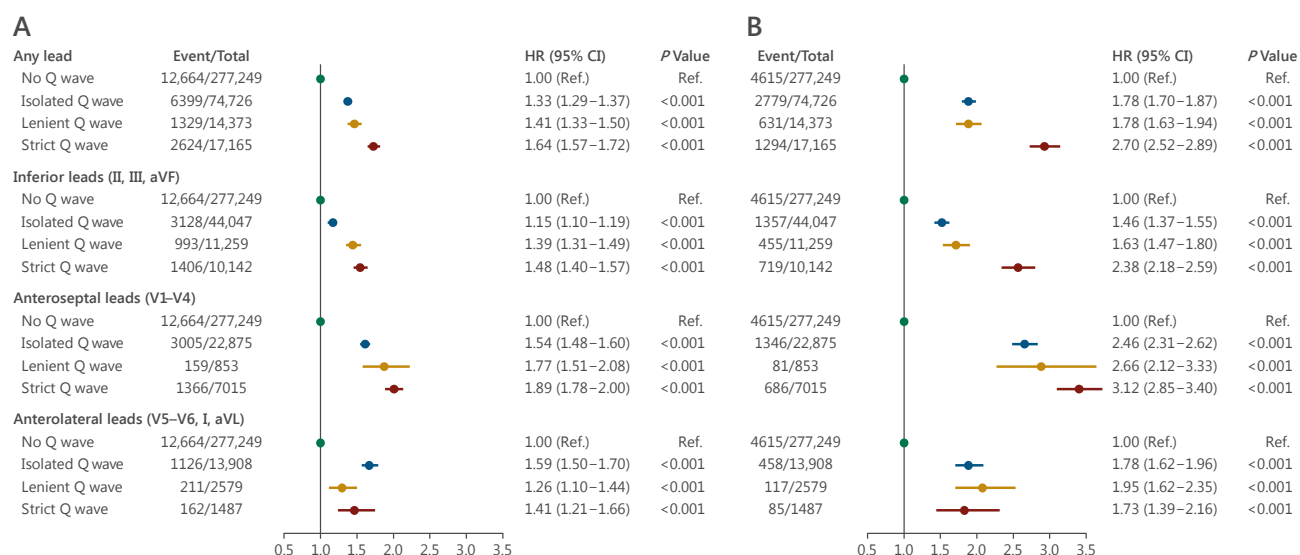
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**Figure 1:** Definitions and representative examples of no (A), isolated (B), lenient (C), or strict (D) Q waves.



**Figure 2:** Cumulative incidence of 2-year all-cause mortality for no, isolated, lenient, or strict Q waves by any two leads of a contiguous lead grouping (A), inferior (B), anteroseptal (C), and anterolateral (D) leads.



**Figure 3:** Association of isolated, lenient, or strict Q waves with 2-year all-cause (A) and cardiovascular (B) mortality risk compared with no Q waves by any two leads of a contiguous lead grouping, inferior, anteroseptal, and anterolateral leads.

Adjusted for age quartiles, sex, heart failure, myocardial infarction, atrial fibrillation, valvular heart disease, hypertension, lipid-lowering drugs, diabetes, chronic obstructive pulmonary disease, and chronic kidney disease.

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Abbreviations: CI, confidence interval; HR, hazard ratio.

**Table 1:** Q-Wave Criteria According to the Fourth Universal Definition of Myocardial Infarction.<sup>8</sup>

Any Q wave in leads V2–V3 >20 ms or QS complex in leads V2–V3
Q wave $\geq 30$ ms and $\geq 1$ mm or QS complex in leads I, II, aVL, aVF, or V4–V6 in any two leads of a contiguous lead grouping (I, aVL; V1–V6; II, III, aVF)
R wave >40 ms in leads V1–V2 and R/S >1 with a concordant positive T wave

**Table 2:** Patient Characteristics.

	Isolated, Lenient, or Strict Q Waves (n=87,957)	No Q Wave (n=277,249)	P Value
Demographics			
Age, years	61.0 [48.0–73.0]	53.0 [40.0–66.0]	<0.001

Sex (male)	41,770 (47.5)	115,973 (41.8)	<0.001
ECG characteristics			
Heart rate, bpm	71.0 [63.0–81.0]	69.0 [62.0–78.0]	<0.001
P-wave duration, ms	110.0 [102.0–118.0]	108.0 [100.0–116.0]	<0.001
PR interval, ms	162.0 [146.0–180.0]	154.0 [142.0–170.0]	<0.001
QRS duration, ms	90.0 [84.0–100.0]	90.0 [84.0–98.0]	0.025
QT interval, ms	394.0 [374.0–414.0]	394.0 [376.0–414.0]	<0.001
Fridericia-corrected QT interval, ms	416.0 [403.0–430.0]	414.0 [402.0–427.0]	<0.001
Comorbidities			
Heart failure	3890 (4.4)	4200 (1.5)	<0.001
Myocardial infarction	6014 (6.8)	5511 (2.0)	<0.001
Atrial fibrillation	3112 (3.5)	6018 (2.2)	<0.001
Valvular heart disease	1129 (1.3)	1578 (0.6)	<0.001
Hypertension	18,417 (20.9)	33,512 (12.1)	<0.001
Diabetes	10,679 (12.1)	18,994 (6.9)	<0.001
Chronic obstructive pulmonary disease	10,555 (12.0)	24,869 (9.0)	<0.001
Chronic kidney disease	2134 (2.4)	4757 (1.7)	<0.001
Cardiovascular drugs			
Loop diuretics	6461 (7.3)	9607 (3.5)	<0.001
Thiazide diuretics	10,960 (12.5)	22,145 (8.0)	<0.001
ACEIs or ARBs	22,219 (25.3)	43,045 (15.5)	<0.001
Mineralocorticoid receptor antagonists	1373 (1.6)	1985 (0.7)	<0.001
Beta blockers	10,800 (12.3)	20,504 (7.4)	<0.001
Calcium channel blockers	12,587 (14.3)	24,421 (8.8)	<0.001
Antianginal drugs	2834 (3.2)	3755 (1.4)	<0.001
Antiplatelets	17,005 (19.3)	27,631 (10.0)	<0.001
Lipid-lowering drugs	16,889 (19.2)	31,922 (11.5)	<0.001
Values reported as median [25th–75th percentiles] or <i>n</i> (%). <i>P</i> Values based on Mann-Whitney U and chi-squared tests, as appropriate.			
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; bpm, beats per minute.			